

King's Research Portal

DOI:

[10.1016/j.biopsych.2018.04.023](https://doi.org/10.1016/j.biopsych.2018.04.023)

Document Version

Publisher's PDF, also known as Version of record

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Karolinska Schizophrenia Project, van Erp, T. G. M., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., Pearlson, G. D., Yao, N., Fukunaga, M., Hashimoto, R., Okada, N., Yamamori, H., Bustillo, J. R., Clark, V. P., Agartz, I., Mueller, B. A., Cahn, W., de Zwarte, S. M. C., ... Dima, D. (2018). Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. *Biological psychiatry*, 84(9), 644-654.
<https://doi.org/10.1016/j.biopsych.2018.04.023>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium

Theo G.M. van Erp, Esther Walton, Derrek P. Hibar, Lianne Schmaal, Wenhao Jiang, David C. Glahn, Godfrey D. Pearlson, Nailin Yao, Masaki Fukunaga, Ryota Hashimoto, Naohiro Okada, Hidenaga Yamamori, Juan R. Bustillo, Vincent P. Clark, Ingrid Agartz, Bryon A. Mueller, Wiepke Cahn, Sonja M.C. de Zwarte, Hilleke E. Hulshoff Pol, René S. Kahn, Roel A. Ophoff, Neeltje E.M. van Haren, Ole A. Andreassen, Anders M. Dale, Nhat Trung Doan, Tiril P. Gurholt, Cecilie B. Hartberg, Unn K. Haukvik, Kjetil N. Jørgensen, Trine V. Lagerberg, Ingrid Melle, Lars T. Westlye, Oliver Gruber, Bernd Kraemer, Anja Richter, David Zilles, Vince D. Calhoun, Benedicto Crespo-Facorro, Roberto Roiz-Santiañez, Diana Tordesillas-Gutiérrez, Carmel Loughland, Vaughan J. Carr, Stanley Catts, Vanessa L. Cropley, Janice M. Fullerton, Melissa J. Green, Frans A. Henskens, Assen Jablensky, Rhoshel K. Lenroot, Bryan J. Mowry, Patricia T. Michie, Christos Pantelis, Yann Quidé, Ulrich Schall, Rodney J. Scott, Murray J. Cairns, Marc Seal, Paul A. Tooney, Paul E. Rasser, Gavin Cooper, Cynthia Shannon Weickert, Thomas W. Weickert, Derek W. Morris, Elliot Hong, Peter Kochunov, Lauren M. Beard, Raquel E. Gur, Ruben C. Gur, Theodore D. Satterthwaite, Daniel H. Wolf, Aysenil Belger, Gregory G. Brown, Judith M. Ford, Fabio Macciardi, Daniel H. Mathalon, Daniel S. O'Leary, Steven G. Potkin, Adrian Preda, James Voyvodic, Kelvin O. Lim, Sarah McEwen, Fude Yang, Yunlong Tan, Shuping Tan, Zhiren Wang, Fengmei Fan, Jingxu Chen, Hong Xiang, Shiyong Tang, Hua Guo, Ping Wan, Dong Wei, Henry J. Bockholt, Stefan Ehrlich, Rick P.F. Wothhusen, Margaret D. King, Jody M. Shoemaker, Scott R. Sponheim, Lieuwe De Haan, Laura Koenders, Marise W. Machielsen, Therese van Amelsvoort, Dick J. Veltman, Francesca Assogna, Nerisa Banaj, Pietro de Rossi, Mariangela Iorio, Fabrizio Piras, Gianfranco Spalletta, Peter J. McKenna, Edith Pomarol-Clotet, Raymond Salvador, Aiden Corvin, Gary Donohoe, Sinead Kelly, Christopher D. Whelan, Erin W. Dickie, David Rotenberg, Aristotle N. Voineskos, Simone Ciufolini, Joaquim Radua, Paola Dazzan, Robin Murray, Tiago Reis Marques, Andrew Simmons, Stefan Borgwardt, Laura Egloff, Fabienne Harrisberger, Anita Riecher-Rössler, Renata Smieskova, Kathryn I. Alpert, Lei Wang, Erik G. Jönsson, Sanne Koops, Iris E.C. Sommer, Alessandro Bertolino, Aurora Bonvino, Annabella Di Giorgio, Emma Neilson, Andrew R. Mayer, Julia M. Stephen, Jun Soo Kwon, Je-Yeon Yun, Dara M. Cannon, Colm McDonald, Irina Lebedeva, Alexander S. Tomyshev, Tolibjohn Akhadow, Vasily Kaleda, Helena Fatouros-Bergman, Lena Flyckt, Karolinska Schizophrenia Project, Geraldo F. Busatto, Pedro G.P. Rosa, Mauricio H. Serpa, Marcus V. Zanetti, Cyril Hoschl, Antonin Skoch, Filip Spaniel, David Tomecek, Saskia P. Hagenaars, Andrew M. McIntosh, Heather C. Whalley, Stephen M. Lawrie, Christian Knöchel, Viola Oertel-Knöchel, Michael Stäblein, Fleur M. Howells, Dan J. Stein, Henk S. Temmingh, Anne Uhlmann, Carlos Lopez-Jaramillo, Danai Dima, Agnes McMahon, Joshua I. Faskowitz, Boris A. Gutman, Neda Jahanshad, Paul M. Thompson, and Jessica A. Turner

SEE COMMENTARY ON PAGE 626

ABSTRACT

BACKGROUND: The profile of cortical neuroanatomical abnormalities in schizophrenia is not fully understood, despite hundreds of published structural brain imaging studies. This study presents the first meta-analysis of cortical thickness and surface area abnormalities in schizophrenia conducted by the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) Schizophrenia Working Group.

METHODS: The study included data from 4474 individuals with schizophrenia (mean age, 32.3 years; range, 11–78 years; 66% male) and 5098 healthy volunteers (mean age, 32.8 years; range, 10–87 years; 53% male) assessed with standardized methods at 39 centers worldwide.

RESULTS: Compared with healthy volunteers, individuals with schizophrenia have widespread thinner cortex (left/right hemisphere: Cohen's $d = -0.530/-0.516$) and smaller surface area (left/right hemisphere: Cohen's $d = -0.251/-0.254$), with the largest effect sizes for both in frontal and temporal lobe regions. Regional group differences in cortical thickness remained significant when statistically controlling for global cortical thickness, suggesting regional specificity. In contrast, effects for cortical surface area appear global. Case-control, negative, cortical thickness effect sizes were two to three times larger in individuals receiving antipsychotic medication relative to unmedicated individuals. Negative correlations between age and bilateral temporal pole thickness were stronger in individuals with schizophrenia than in healthy volunteers. Regional cortical thickness showed significant negative correlations with normalized medication dose, symptom severity, and duration of illness and positive correlations with age at onset.

CONCLUSIONS: The findings indicate that the ENIGMA meta-analysis approach can achieve robust findings in clinical neuroscience studies; also, medication effects should be taken into account in future genetic association studies of cortical thickness in schizophrenia.

Keywords: Cortical, Imaging, Meta-analysis, Schizophrenia, Surface area, Thickness

<https://doi.org/10.1016/j.biopsych.2018.04.023>

Brain structural abnormalities are widely reported in schizophrenia, but there is no published meta-analysis reporting effect sizes for cortical thickness and surface area abnormalities and their relationships to clinical features of the disease. Several hundred studies have reported on cortical thickness and surface area abnormalities in schizophrenia, but it is difficult to meta-analyze published results, as they lack a standard format to ease comparisons and are based on atlas (1) or vertex-wise (2) approaches using a variety of methods (3–9). To address these issues, the Schizophrenia Working Group within the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis; <http://enigma.ini.usc.edu>) (10–12) consortium brings together schizophrenia researchers from all over the world to jointly conduct large-scale imaging and imaging/genetics meta-analyses using standardized methods.

This meta-analysis focuses on regional cortical thickness and surface area rather than volume, based on evidence that they are influenced by separate sets of genes (13,14). Cortical thickness and surface area abnormalities have been reported in individuals with chronic (1,15–17), short- or medium-duration (18), first-episode (19–24), child-onset (25,26), adolescent-onset (27), and antipsychotic-naïve (28–30) schizophrenia; individuals with nonclinical psychotic symptoms (31); and individuals at clinical high risk for psychosis (32–39).

We previously reported effect sizes for deep brain structure volume abnormalities based on 15 samples worldwide, including brain imaging data from 2028 individuals with schizophrenia and 2540 healthy volunteers (40); findings were replicated in an independent cohort using similar methods (41). Here we report Cohen's d effect sizes comparing regional cortical thickness and surface area between 4474 individuals

with schizophrenia and 5098 healthy volunteers, and partial correlation effect sizes with continuous clinical measures based on 39 worldwide samples. Based on prior work, we hypothesized that individuals with schizophrenia, compared with healthy volunteers, show widespread cortical thickness and surface abnormalities that are most prominent in frontal and temporal lobe regions (15) and that show significant associations with age at onset or duration of illness (42), symptom severity (43–48), and antipsychotic medication use (49–51).

METHODS AND MATERIALS**Study Samples**

Via the ENIGMA Schizophrenia Working Group, 39 worldwide, cross-sectional study samples totaling 9572 participants, including 4474 individuals with schizophrenia and 5098 healthy volunteers, contributed to the analysis (Tables S1a and S1b and Figure S1 in Supplement 1). Sample-size weighted mean (range) age across samples was 32.3 (21.2–43.6) years for individuals with schizophrenia and 34.5 (21.8–43.9) years for healthy volunteers. Patient and control samples were on average 65% (44–100) and 54% (36–100) male. Weighted mean age at onset and duration of illness across the samples were 23.4 (20.0–35.6) years and 10.5 (0.6–20.2) years. Weighted mean Positive and Negative Syndrome Scale (PANSS) (52) total, negative, and positive scores across the samples were 68.1 (43.0–90.2), 21.9 (10.0–22.9), and 16.4 (10.6–22.6); weighted mean Scale for the Assessment of Negative Symptoms (53) and Scale for the Assessment of Positive Symptoms (54) scores were 20.5 (5.5–33.0) and 19.2

(9.0–32.3), respectively. For samples that recorded current antipsychotic type and/or dose, numbers (percentages) of patients on second-generation (atypical), first-generation (typical), both second-generation and first-generation, or no (unmedicated) antipsychotic medications were 2236 (66%), 447 (13%), 265 (8%), and 425 (13%), and sample-size weighted mean chlorpromazine dose equivalent, based on Woods' calculations (www.scottwilliamwoods.com/files/Equivtext.doc), was 399 (167–643). Each study sample was collected with participants' written informed consent approved by local institutional review boards.

Image Acquisition and Processing

All sites processed T1-weighted structural brain scans using FreeSurfer (9) (<http://surfer.nmr.mgh.harvard.edu>) and extracted cortical thickness and surface area for 70 Desikan-Killiany (DK) atlas regions (55) (34 regions per hemisphere + left and right hemisphere mean thickness or total surface area) (Table S3 in Supplement 1). Number of scanners, vendor, strength, sequence, acquisition parameters, and FreeSurfer versions are provided in Table S2 in Supplement 1. ENIGMA's quality assurance protocol was performed at each site before analysis and included visual checks of the cortical segmentations and region-by-region removal of values for segmentations found to be incorrect (<http://enigma.usc.edu/protocols/imaging-protocols>) (Table S2 in Supplement 1). Histograms of all regions' values for each site were also computed for visual inspection.

Statistical Meta-analyses

Group differences for DK atlas regions within each sample were examined using univariate linear regression (R linear model function `lm`; R Foundation for Statistical Computing, Vienna, Austria) predicting left and right DK atlas region cortical thickness or surface area with group (individuals with schizophrenia, healthy volunteers), gender, and age (model A). To further assess whether group differences in cortical thickness and surface area showed regional specificity, analyses were repeated including global mean cortical thickness and total cortical surface area as covariates, respectively (model B). To test for differential gender or age effects between groups, we also included models with group-by-gender (model C) or group-by-age interaction terms (model D). Significant interactions were further explored through within-group analyses. Medication effects were examined through between-

group comparisons of individuals with schizophrenia on second-generation (atypical), first-generation (typical), both second-generation and first-generation, or no (unmedicated) antipsychotic medications and healthy volunteers with gender and age included as covariates; only contrasts with a minimum of 5 subjects per group within site were included in these analyses to enable variance estimation. In patients, relationships were examined between regional cortical measures and several continuous variables, including age at onset; duration of illness; chlorpromazine equivalent antipsychotic medication dose; and total, positive, and negative symptom severity. These partial correlation analyses included age and gender as covariates. Analysis of multisite studies (ASRB, FBIRN, MCIC, Osaka, UPENN) included binary dummy covariates for $n-1$ scanners. Sites conducted analyses of their sample's individual subject data using R code created within the ENIGMA collaboration. Random-effects meta-analyses of Cohen's d and partial correlation effect sizes for each of the DK atlas regions were performed using R (version 3.2.2) metafor package (version 1.9-7) (56). False discovery rate (FDR) ($p_{FDR} < .05$) (57) was used to control for multiple comparisons. Cortical maps depict significant effect sizes ($p_{FDR} < .05$) overlaid on (metallic gray) cortical surface models (<https://brainder.org/research/brain-for-blender>). Possible confounding effects of differences in parental socioeconomic status on group differences were examined using subsample analyses (see Results SR3, Figures, and Tables S8a and S9b, and S52a and S53b in Supplement 1). Effects of FreeSurfer version and scanner field strength were examined using meta-regressions (Supplement 1).

RESULTS

Widespread Thinner Cortex With Regional Specificity in Schizophrenia

Individuals with schizophrenia, compared with healthy volunteers, showed widespread significantly thinner cortex in all DK atlas regions except the bilateral pericalcarine region (model A), with effect sizes between Cohen's $d = -0.536$ (right fusiform gyrus) and Cohen's $d = -0.077$ (left pericalcarine fissure) and marginal (least square) mean thickness differences between -3.33% (left parahippocampal gyrus) and -0.45% (left pericalcarine fissure) (Figure 1A and Table S4a in Supplement 1). The largest negative effect sizes (Cohen's $d < -0.40$) were observed for left/right hemisphere (Cohen's $d = -0.530/-0.516$); bilateral fusiform, temporal (inferior,

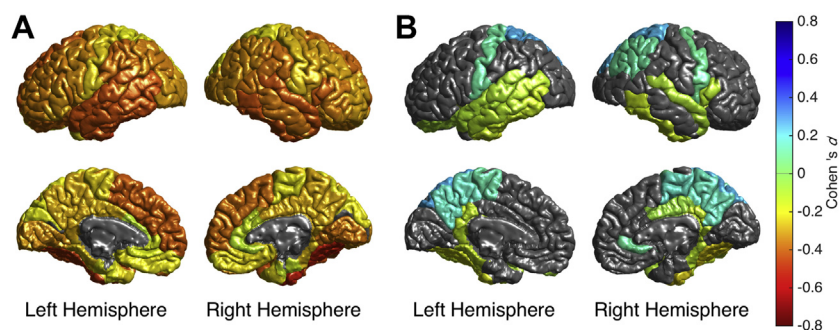


Figure 1. Cortical map of regional Cohen's d effect sizes for schizophrenia subjects' vs. healthy volunteers' cortical thickness contrast statistically controlling for age and gender (A) and age, gender, and global cortical thickness (B). Only regions with $p_{\text{false discovery rate}} < .05$ are depicted in color. In panel (B), warm colors (yellow-red) reflect regions in which the effect of schizophrenia is more than the mean global cortical thinning, and cool colors (green-blue) reflect regions where the effect of schizophrenia is less than the mean global thinning compared with healthy volunteers.

middle, and superior), and left superior frontal gyri; right pars opercularis; and bilateral insula.

In the context of widespread thinner cortex in schizophrenia, we assessed regional specificity of these cortical thickness differences. When controlling for individual differences in global mean cortical thickness, several regions showed significantly thinner cortex (e.g., fusiform, parahippocampal, inferior temporal gyri), whereas other regions showed significantly thicker cortex (e.g., superior parietal cortex, precuneus, paracentral lobule) in individuals with schizophrenia compared with healthy volunteers (model B) (Figures 1B and Figure 2; Table S4b in Supplement 1). These findings suggest regional specificity of thinner cortex in schizophrenia.

Widespread Smaller Cortical Surface Area Without Regional Specificity in Schizophrenia

Individuals with schizophrenia, compared with healthy individuals, showed widespread significantly smaller cortical surface area in all DK atlas regions except the bilateral isthmus cingulate region (model A), with effect sizes between Cohen's $d = -0.254$ (mean right hemisphere) and Cohen's $d = -0.040$ (right isthmus cingulate) and marginal (least square) mean surface area differences between -3.39% (left rostral anterior cingulate) and -0.55% (right isthmus cingulate) (Figure 3A; Table S5a in Supplement 1). The largest effect sizes (Cohen's $d < -0.20$) were observed for left (Cohen's $d = -0.251$) and right (Cohen's $d = -0.254$) hemisphere and bilateral superior frontal, fusiform, inferior and middle temporal, and right precentral gyri.

In the context of widespread smaller cortical surface area in schizophrenia, we assessed regional specificity of these cortical surface area differences. When controlling for individual differences in total cortical surface area, no regions showed significantly smaller surface area, whereas three regions showed significantly larger cortical surface area (bilateral isthmus cingulate, precuneus, and left paracentral) in individuals with schizophrenia compared with healthy volunteers

(model B) (Figure 3B; Table S5b in Supplement 1). These findings suggest that smaller cortical surface area is predominantly global in schizophrenia except for the three regions noted, which appear less affected.

Group-by-Gender Interactions

No significant group-by-gender interactions were detected for either cortical thickness or surface area for any of the DK atlas regions (Tables S6 and S7 in Supplement 1).

Group-by-Age Interactions

There were significant group-by-age interactions for both left ($p_{FDR} = .007$) and right ($p_{FDR} = .01$) temporal pole thickness, with individuals with schizophrenia showing stronger negative correlations with age (left, $r = -.13$, $p_{FDR} = 1.51E-13$; right, $r = -.12$, $p_{FDR} = 1.55E-07$) than healthy volunteers (left, $r = -.05$, $p_{FDR} = .02$; right, $r = -.04$, $p_{FDR} = .03$). These interactions remained significant even when controlling for global mean cortical thickness (Figure S2 and Tables S8a, S8b, S10, and S11 in Supplement 1). There were no significant group-by-age interactions for cortical surface area for any of the DK atlas regions (Table S9 in Supplement 1).

Partial Correlations With Age of Onset and Duration of Illness

Earlier age of onset ($r = .063$, $p_{FDR} = .03$) and longer duration of illness ($r = -.061$, $p_{FDR} = .04$) were significantly correlated with thinner right insula cortical thickness (Tables S33 and S34 and Figure S3 in Supplement 1). There were no significant correlations between age of onset or duration of illness and cortical surface area for any of the DK atlas regions (Tables S43 and S44 in Supplement 1).

Effects of Antipsychotic Medications on Cortical Thickness

Effect sizes comparing left and right hemisphere cortical thickness from individuals with schizophrenia on no

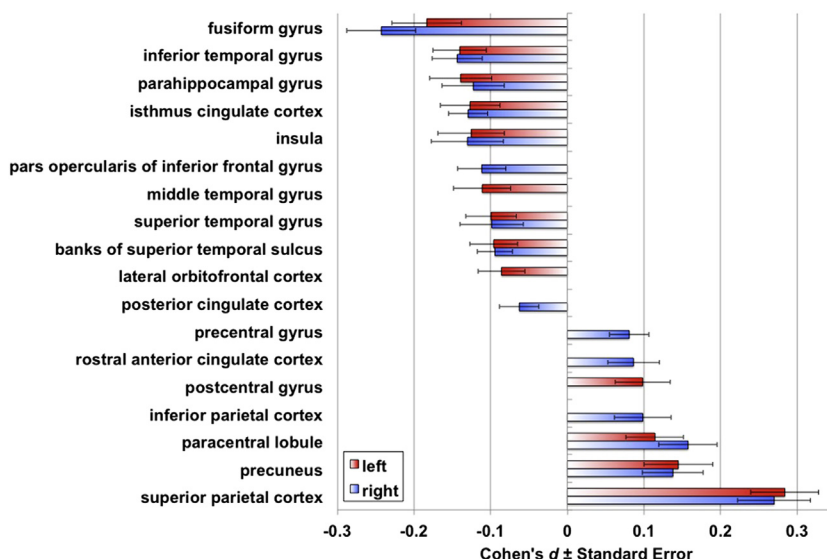
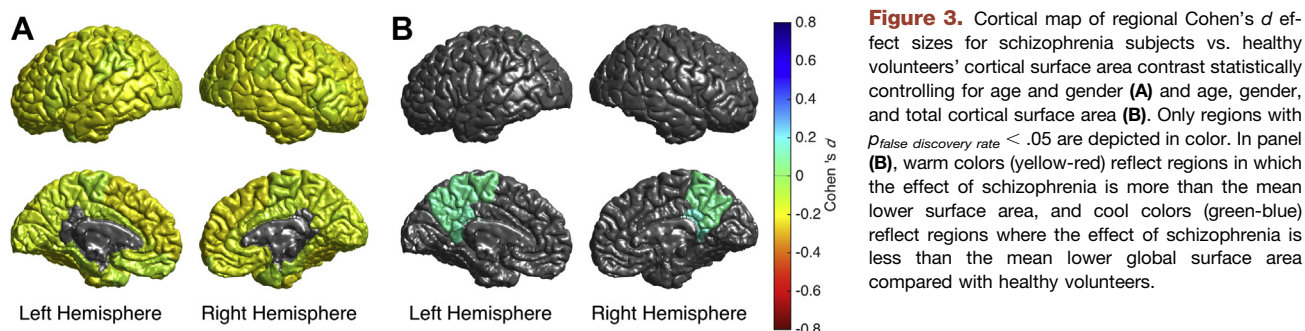


Figure 2. Cohen's d effect sizes for schizophrenia subjects' vs. healthy volunteers' cortical thickness contrast statistically controlling for age, gender, and global mean cortical thickness. Only regions with $p_{false\ discovery\ rate} < .05$ are depicted in color.



(unmedicated; left/right, Cohen's $d = -0.275/-0.278$), second-generation (left/right, Cohen's $d = -0.536/-0.516$), first-generation (left/right, Cohen's $d = -0.765/-0.648$), or both second-generation and first-generation (left/right Cohen's $d = -0.770/-0.704$) antipsychotic medications with healthy volunteers were significant for all but the unmedicated group ($p_{FDR} > .05$) (Figure 4; Tables S12–S15 in Supplement 1).

Groupwise comparisons of left and right hemisphere thickness found nominally significant effects for all medicated versus unmedicated groups (Figure 4; Tables S16–S18 in Supplement 1). Similarly, nominally significant effects were found for first-generation versus second-generation and both second-generation and first-generation versus second-generation medication groups, but not both versus first-generation medication groups (Figure 4; Tables S19–S21 in Supplement 1). No significant regional effects were observed for the last four group contrasts ($p_{FDR} > .05$) (Tables S18–S21 in Supplement 1). For detailed regional effects of antipsychotic

medications on cortical thickness and surface area, see Results SR1 in Supplement 1.

Partial Correlations With Medication Dose

Higher chlorpromazine dose equivalents were significantly correlated with thinner cortex in almost all the DK atlas regions except bilateral entorhinal and pericalcarine cortex; bilateral lingual and transverse temporal gyri; left postcentral, cuneus, and parahippocampal gyri; caudal anterior cingulate cortex; right superior parietal and rostral anterior cingulate cortex; and right frontal pole (Figure S6A and Table S32 in Supplement 1). The correlations were significant for both left ($r = -.126$) and right ($r = -.126$) hemisphere thickness and were strongest (partial $r < -.10$) for left ($r = -.166$) and right ($r = -.148$) superior frontal, left ($r = -.113$) and right ($r = -.108$) middle temporal, left ($r = -.112$) and right ($r = -.106$) superior temporal, right inferior temporal ($r = -.113$), right pars triangularis of inferior frontal ($r = -.113$), left ($r = -.102$) and right ($r = -.108$) caudal middle frontal, and left supramarginal ($r = -.103$) gyri.

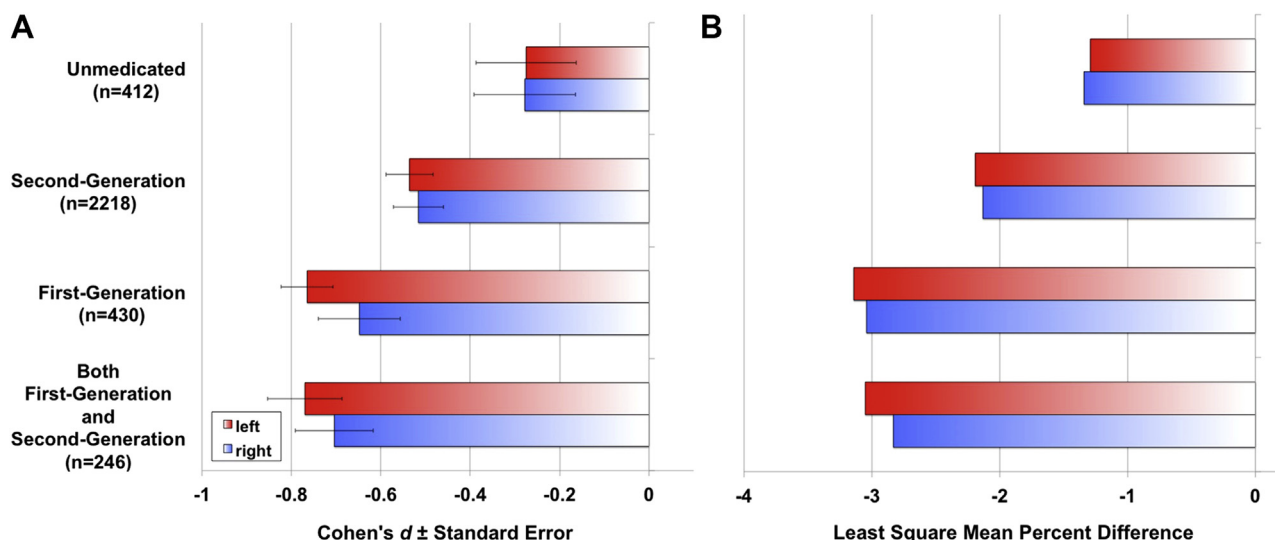


Figure 4. Cohen's d effect sizes (A) and least square mean percent difference (B) for schizophrenia subjects vs. healthy volunteers contrasts in global cortical thickness statistically controlling for age and gender by medication group and hemisphere. Nominal one-tailed p values for left and right hemisphere thickness group comparisons statistically controlling for age and gender were as follows: second-generation vs. unmedicated (left, $p < .05$; right, $p < .06$); first-generation vs. unmedicated (left, $p < .01$; right, $p < .002$); both first-generation and second-generation vs. unmedicated (left, $p < .02$; right, $p < .05$); first-generation vs. second-generation (left, $p < .03$; right, $p < .03$); both first-generation and second-generation vs. second-generation (left, $p < .02$; right, $p < .05$); both first-generation and second-generation vs. first-generation (left, $p = .50$; right, $p = .48$) (Tables S16–S21 in Supplement 1).

Importantly, post hoc analysis showed that higher chlorpromazine dose equivalents were significantly correlated with thinner cortex even when controlling for negative symptom severity (Table S41 and Figure S7 in Supplement 1). There were no detectable correlations between chlorpromazine dose equivalents and cortical surface area for any of the DK atlas regions (Table S42 in Supplement 1).

Partial Correlations With Symptom Severity Scores

Higher PANSS total and positive symptom severity scores were significantly correlated with regional thinner cortex (Figure S6B, Table S35, Figure S6D, and Table S36 in Supplement 1), whereas higher PANSS negative symptom scores were significantly correlated with widespread thinner cortex in left ($r = -.085$) and right ($r = -.089$) hemispheres (Figure S6C and Table S37 in Supplement 1; see Results SR2 in Supplement 1 for details). PANSS total, positive, and negative symptom severity scores were not significantly correlated with regional cortical surface area for any of the DK atlas regions (Tables S45–S47 in Supplement 1).

DISCUSSION

The main findings of this study are that individuals with schizophrenia, compared with healthy volunteers, show the following: 1) widespread thinner cortex (left/right, Cohen's $d = -.530/-0.516$); 2) widespread smaller cortical surface area, about half the size of the effect observed for cortical thickness (left/right Cohen's $d = -.251/-0.254$); 3) the largest effect sizes in frontal and temporal lobe regions for both measures, with regional specificity for cortical thickness, but not cortical surface area (based on the analyses controlling for global thickness and surface area); 4) approximately two times larger negative cortical thickness effect size when on second-generation antipsychotic medications (left/right, Cohen's $d = -.536/-0.516$) and approximately three times larger cortical thickness effect size when on first-generation (left/right, Cohen's $d = -.765/-0.648$) or both first-generation and second-generation (left/right, Cohen's $d = -.770/-0.704$) antipsychotic medications relative to unmedicated individuals with schizophrenia (left/right, Cohen's $d = -.275/-0.278$); and 5) a stronger negative correlation between age and bilateral temporal pole cortical thickness (left, $r = -.13$ vs. $r = -.05$; right, $r = -.12$ vs. $r = -.04$). With regard to partial correlations with clinical variables, 6) earlier age at onset and longer duration of illness were associated with thinner insula cortex; 7) standardized medication dose (chlorpromazine dose equivalent) and 8) negative symptom severity were associated with widespread thinner cortex; and 9) total and 10) positive symptom severity were associated with regional thinner cortex. Most observed correlations were small ($r < .2$). Moreover, despite the high power to detect small effects, medication use and other clinical variables were not significantly associated with cortical surface area.

These findings are consistent with the interpretation that the thinner cortex observed in individuals with schizophrenia shows regional specificity and is associated with the disease (28–30), its severity (43–48), and antipsychotic medication treatment (49–51), with a larger effect for first-generation compared with second-generation antipsychotic medications

(16,58–60). We cannot fully exclude the possibility that observed medication effects on cortical thickness are partially due to group differences in age or duration of illness (61), which also show patterns of increase across the groups. However, such an interpretation is rendered unlikely by the facts that 1) age was statistically controlled for in the medication type analyses; 2) duration of illness, which is highly collinear with age, showed effects above and beyond age only on right insula thickness; 3) there was only a group-by-age interaction on temporal pole thickness (while medication effects were widespread); and 4) meta-regressions showed no effects of age or duration of illness on group contrast effect sizes (see Results SR1 in Supplement 1). Furthermore, dissociating medication effects from other potentially confounding variables requires well-powered, first-episode longitudinal studies, preferably with random assignment to first-generation or second-generation antipsychotics. Two longitudinal imaging studies that randomly assigned individuals to medication treatments found significant gray matter reductions for haloperidol but not olanzapine (58,62); these findings are consistent with our meta-analysis and with reported medication effects on cortical thickness in rodents (63).

None of the other potential confounding variables, including gender distribution, age at onset, medication dose, global symptoms, negative symptoms, or positive symptoms, showed a pattern consistent with the observed medication effects. These variables are therefore unlikely to explain the differences in cortical thickness effect sizes across the antipsychotic medication groups on their own, although more complex interactions could exist. In contrast to thinner cortex, smaller cortical surface area in individuals with schizophrenia appears to be a more global phenomenon associated with the disease, but not with its severity or its treatment. It is possible that more focal cortical surface area effects are obfuscated through the averaging of measurements within DK atlas regions; vertexwise analyses may have higher power for detecting and localizing such effects.

This study found significant group-by-age interactions on cortical thickness in the bilateral temporal pole regions only, with a stronger negative correlation between age and cortical thickness in individuals with schizophrenia than in healthy volunteers. In addition, this study found that earlier age at onset and longer duration of illness were associated with thinner cortical thickness in the insula only. These findings corroborate reported longitudinal findings of lower cortical volumes at illness onset as well as progressive volume decline in the temporal pole and insula in individuals with schizophrenia (64,65) and individuals at ultra-high risk for psychosis (66). Given our results, these volume declines may reflect cortical thinning rather than cortical surface area reduction. While our findings may suggest that there are few differential effects of age on cortical thickness between individuals with schizophrenia and healthy volunteers, we must keep in mind that age effects on thickness across a large age range are nonlinear (67) and that this meta-analysis combines linear age effects across multiple independent cross-sectional cohorts of various ages. Longitudinal studies are better poised to address the question of differential effects of age and duration of illness on cortical thickness in schizophrenia, and some have observed steeper rates of cortical thinning in multiple regions

in individuals with schizophrenia and their non-ill co-twins (61). ENIGMA Schizophrenia Working Group members are actively working on pooling longitudinal studies for a meta-analysis to further address these questions.

Taken together, these findings may suggest that cortical surface area developmental trajectories in psychosis may be predominantly influenced by early neurodevelopmental, perhaps predominantly genetic, factors. In contrast, cortical thickness, in addition to likely being influenced by different genes (13,14), may be more plastic and also influenced by additional environmental and neurodegenerative factors (e.g., treatment, cannabis use, age) (68).

This study found significant widespread associations between standardized medication doses (chlorpromazine equivalents) and cortical thickness but not cortical surface area. This finding is consistent with and extends a prior meta-regression analysis, which reported that higher medication doses are associated with smaller gray matter volume (51). Given our results, the association with volume is likely due to cortical thickness rather than surface area. The finding is also consistent with the larger effect sizes for individuals with schizophrenia who were on antipsychotic medications compared with individuals who were not. An alternative interpretation may be that more severely ill patients receive higher doses of medication given the observed significant associations between symptom severity and regional cortical thickness. However, consistent with medication dose effects on cortical thickness, we found that significant associations between chlorpromazine dose equivalent and cortical thickness were still observed in post hoc partial correlation analyses that statistically controlled for negative symptom severity. In this analysis, we opted to control for negative rather than positive symptom severity, as negative symptoms tend to be less influenced by medication dose than positive symptoms.

We caution that the likelihood that antipsychotic medications are associated with thinner cortex in individuals with schizophrenia should by no means be interpreted as a contraindication for their use in treating patients with severe mental illnesses, including schizophrenia. In fact, a recent study found that medication treatment was associated with thinner cortex and better behavioral performance on a cognitive control task (26% higher d' -context score) (24). Most importantly, antipsychotic medications tend to successfully treat severely debilitating psychotic symptoms, reduce relapse risk following a first-episode break (69), and reduce suicide risk (70). As such, they play a critical role in the treatment of psychosis.

Similar published meta-analyses in bipolar disorder and major depressive disorder, with the same study design and analytical methods, found thinner bilateral frontal, temporal, and parietal lobe cortex in individuals with bipolar disorder with evidence for divergent effects of medication treatments (71) and thinner regional cortex in adults with major depressive disorder and smaller total and regional cortical surface area in adolescents with major depressive disorder (72). Taken together, these very-large-scale studies suggest both similarities and differences in cortical abnormalities observed among these three major psychiatric illnesses.

To our knowledge, this is the first meta-analysis of cortical thickness and surface area abnormalities in schizophrenia. Only

one other schizophrenia study has provided a comprehensive listing of Cohen's d effect sizes for regional cortical thickness abnormalities comparing individuals with schizophrenia, non-ill first-degree relatives, and healthy volunteers (1).

The major strength of the study is its large sample size, which provides sufficient power to detect even small effects (e.g., symptom associations). Weaknesses include the following: 1) the group of unmedicated individuals with schizophrenia does not distinguish never-medicated from unmedicated at time of scan, leaving effect sizes for medication-naïve subjects to be determined; 2) despite the large total sample size, many regional thickness differences between medication subgroups did not survive multiple comparison correction; 3) this study does not examine possible group differences in brain lateralization, though such analyses will be reported on separately; and 4) the analysis of chlorpromazine equivalents did not dissociate first-generation and second-generation antipsychotic medications, which may have dissociable effects on cortical thickness (51,72). Finally, while this meta-analysis is unique in that it standardized image analysis methods across sites, any meta-analysis, including this one, is limited by sources of variation inherent to the analysis of retrospectively collected samples that cannot be fully controlled for. Sample differences include the use of different scanners and different assessments or processes to arrive at diagnosis, age at onset, duration of illness, medication dose and adherence, etc. Meta-analyses control for these differences by summing within-site effects across sites, providing generalized mean effect sizes. Similar to other meta-analyses, this meta-analysis does not control for all variance in assessments that can lower power to detect effects.

Taken together, the findings from this meta-analysis suggest that thinner cortex in schizophrenia shows regional specificity and is affected by the illness, its severity, and treatments with antipsychotic medications, whereas smaller cortical surface area is mainly influenced by widespread effects of the illness possibly mainly influenced by developmental processes. In the context of ENIGMA, these findings suggest that schizophrenia genetic association studies employing cortical thickness as a quantitative trait may need to control for medication effects, whereas studies that employ cortical surface area as a quantitative trait may not need to control for medication effects.

ACKNOWLEDGMENTS AND DISCLOSURES

The ENIGMA project is in part supported by the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health (Grant No. U54EB020403). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Acknowledgments for the various participating data contributors are listed in [Supplement 1](#).

Author contributions are as follows: protocol design, quality testing, and meta-analysis, TGMvE, EW, DPH, LS, and WJ; data collection, processing, analysis, and funding, TGMvE, EW, DPH, LS, WJ, DCG, GDP, NY, MF, RH, NO, HY, JRB, VPC, IA, BAM, WC, SMCdZ, HEHP, RSK, RAO, NEMvH, OAA, AMD, NTD, TPG, CBH, UKH, KNJ, TVL, IM, LTW, OG, BK, AR, DZ, VDC, BC-F, RR-S, MJC, VJC, SCA, JR, VLC, JMFu, MJG, FAH, AJ, RKL, CL, BJM, PTM, CP, YQ, PER, GC, US, RJS, MSe, PAT, CSW, TWW, DWM, EH, PK, LMB, REG, RCG, TDS, DHW, ABeI, GGB, JMFo, FM, DHM, DSO, SGP, AP, JV, KOL, SM, FY, YT, STan, ZW, FF, JC, HX, STang, HG, PW, DW, HJB, SE, RPFw, MDK, JMSh, SRS, LDH, LK, MWM, TvA, DJV, FA, NB, PdR, MI, FP,

GS, PJM, EP-C, JR, RSa, AC, GD, SKe, CDW, EWD, DR, ANV, SCi, PD, RM, TRM, ASi, SB, LE, FHa, AR-R, RSm, KIA, LW, EGJ, SKo, IECS, ABer, ABo, ADG, EN, ARM, JMSt, JSK, J-YY, DMC, CM, IL, AST, TA, VK, HF-B, LF, GFB, PGPR, MHS, MVZ, CH, Ask, FS, DT, SPH, AMM, HCW, SML, CK, VO-K, MSt, FMH, DJS, HST, AU, CL-J, DD, AM, JIF, BAG, NJ, PMT, and JAT; manuscript preparation, TGMvE, JAT, and PMT. All authors contributed edits and approved the contents of the manuscript.

TGMvE has had a research contract with Otsuka Pharmaceutical. AP has served as a consultant for Boehringer Ingelheim. The remaining authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry and Human Behavior (TGMvE, FM, SGP, AP), University of California, Irvine, Irvine, California; Imaging Genetics and Neuroinformatics Lab (EW, JAT), Department of Psychology (WJ), Georgia State University, Atlanta, Georgia; Imaging Genetics Center (DPH, CDW, AM, JIF, NJ, PMT), Mark and Mary Stevens Neuroimaging & Informatics Institute, Keck School of Medicine of the University of Southern California, Marina del Rey; Janssen Research & Development (DPH); Center for Translational Imaging and Precision Medicine (AMD), San Diego; Departments of Neurosciences (AMD), Radiology (AMD), Psychiatry (AMD, GGB), and Cognitive Science (AMD), University of California, San Diego, La Jolla, California; Department of Psychiatry (DCG, GDP, NY), Yale University, New Haven; Olin Neuropsychiatric Research Center (DCG, GDP, NY), Institute of Living, Hartford Hospital, Hartford, Connecticut; Department of Psychiatry, University of New Mexico (JRB, VPC, VDC); Mind Research Network (VPC, VDC, HJB, MDK, JMSh, ARM, JMSt, JAT), Albuquerque, New Mexico; Department of Psychiatry (BAM, KOL, SRS), University of Minnesota; Minneapolis VA Health Care System (SRS), Minneapolis, Minnesota; Semel Institute for Neuroscience and Human Behavior (RAO) and Department of Psychiatry & Biobehavioral Sciences (SM), University of California, Los Angeles, Los Angeles, California; Maryland Psychiatric Research Center (EH, PK), University of Maryland School of Medicine, Baltimore, Maryland; Department of Psychiatry (LMB, REG, RCG, TDS, DHW), University of Pennsylvania, Philadelphia, Pennsylvania; Department of Psychiatry (ABel), University of North Carolina at Chapel Hill, Chapel Hill; Brain Imaging and Analysis Center (ABel, JV), Duke University Medical Center, Durham, North Carolina; Department of Psychiatry, Weill Institute for Neurosciences, University of California, San Francisco (JMFO, DHM); San Francisco Veterans Affairs Medical Center (JMFO, DHM), San Francisco, California; Department of Psychiatry (DSO, HJB), University of Iowa; Advanced Biomedical Informatics Group, LLC (HJB), Iowa City, Iowa; Social Neuroscience Laboratory (RPFw), Athinoula A. Martinos Center for Biomedical Imaging (SE), Charlestown; Psychiatric Neuroimaging Research Program (RPFw) and Department of Psychiatry (RPFw), Massachusetts General Hospital, Harvard Medical School; Department of Psychiatry (SKe), Beth Israel Deaconess Medical Center, Harvard Medical School; Psychiatry Neuroimaging Laboratory (SKe), Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; Beth K. and Stuart C. Yudofsky Division of Neuropsychiatry (GS), Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas; Departments of Psychiatry and Behavioral Sciences (KIA, LW) and Radiology (LW), Northwestern University Feinberg School of Medicine; Department of Biomedical Engineering (BAG), Illinois Institute of Technology, Chicago, Illinois; Orygen (LS), The National Centre of Excellence in Youth Mental Health; Centre for Youth Mental Health (LS), Neuropsychiatry Centre (VLC, CP), and Florey Institute of Neuroscience and Mental Health (CP), University of Melbourne; Department of Psychiatry, Monash University (VJC); Murdoch Children's Research Institute (MSe), Melbourne, Victoria; School of Biomedical Sciences and Pharmacy (RJS, MJC, PAT), Priority Research Centre for Health Behaviour (FAH), School of Medicine and Public Health (FAH), School of Psychology (PTM), Priority Research Centre for Brain & Mental Health (CL, US, PAT, PER, GC), and Grow Up Well (US), University of Newcastle; Hunter Medical Research Institute (CL, FAH, US, RJS, MJC, PAT); Hunter New England Local Health District (CL), Newcastle; School of Psychiatry (VJC, MJG, RKL, YQ, CSW, TWW) and School of Medical Sciences (JMfu), University of New South Wales, New South Wales; Neuroscience Research Australia (JMfu, MJG, RKL, YQ, CSW, TWW), Sydney,

New South Wales; Queensland Brain Institute (BJM) and Queensland Centre for Mental Health Research (BJM), Discipline of Psychiatry, School of Medicine, University of Queensland (SCa), Brisbane, Queensland; School of Psychiatry and Clinical Neurosciences, University of Western Australia (AJ), Perth, Western Australia, Australia; Department of Psychiatry and Neuroscience (LS), VU University Medical Center; Department of Psychiatry (LDH, LK, MWM), Academic Medical Center, University of Amsterdam; Department of Psychiatry (DJV), Vrije Universiteit Medical Center, Amsterdam; Department of Child and Adolescent Psychiatry/Psychology (NEMvH), Erasmus Medical Centre, Rotterdam; Departments of Neuroscience (IECS) and Psychiatry (IECS), University Medical Center Groningen, Rijks Universiteit Groningen, Groningen; Department of Psychiatry and Brain Center Rudolf Magnus (WC, SMCdZ, HEHP, NEMvH, RSK, RAO, SKO), University Medical Center Utrecht, Utrecht; Department of Psychiatry & Psychology (TvA), Maastricht University, Maastricht, The Netherlands; Division of Cerebral Integration (MF), National Institute for Physiological Sciences, Okazaki, Aichi; Molecular Research Center for Children's Mental Development (RH), United Graduate School of Child Development, Osaka University; Department of Psychiatry (RH, HY), Osaka University Graduate School of Medicine, Suita, Osaka; Department of Neuropsychiatry (NO), Graduate School of Medicine, University of Tokyo, Bunkyo-ku, Tokyo, Japan; Institute of Clinical Medicine (IA, OAA, NTD, TPG, CBH, UKH, KNJ, IM, EGJ), Norwegian Centre for Mental Disorders Research (NORMENT), K.G. Jebsen Centre for Psychosis Research, and Department of Psychology (LTW), University of Oslo; Division of Mental Health and Addiction (OAA, UKH, TVL, IM, LTW), NORMENT, K.G. Jebsen Centre for Psychosis Research, Oslo University Hospital; Department of Psychiatric Research (IA, KNJ, TGP), Diakonhjemmet Hospital, Oslo, Norway; Centre for Psychiatry Research (HF-B, LF), Department of Clinical Neuroscience (IA, JR, EGJ), Karolinska Institutet; Stockholm Health Services (HF-B, LF), Stockholm County Council, Stockholm, Sweden; Section for Experimental Psychopathology and Neuroimaging (OG, BK, AR), Department of General Psychiatry, Heidelberg University Hospital, Heidelberg; Center for Translational Research in Systems Neuroscience and Psychiatry (OG, BK, AR, DZ), Department of Psychiatry, Georg August University; Department of Psychiatry (DZ), University Medical Center Göttingen, Göttingen; Division of Psychological and Social Medicine and Developmental Neurosciences (SE, RPFw), Faculty of Medicine, Technische Universität Dresden, Dresden; Department of Psychiatry, Psychosomatic Medicine and Psychotherapy (CK, VO-K, MSt), University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany; Department of Psychiatry (BC-F, RR-S, DT-G), University Hospital Marqués de Valdecilla, School of Medicine; Neuroimaging Unit (DT-G), Technological Facilities, Valdecilla Biomedical Research Institute, Marqués de Valdecilla Research Institute (IDIVAL), University of Cantabria; Centro Investigación Biomédica en Red de Salud Mental (BC-F, RR-S, DT-G), Santander; Fundación para la Investigación y Docencia María Angustias Giménez (FIDMAG) Germanes Hospitalaries Research Foundation (PJM, EP-C, RSa, JR); Centro Investigación Biomédica en Red de Salud Mental (PJM, EP-C, RSa, JR), Barcelona, Spain; Centre for Neuroimaging & Cognitive Genomics (DWM, GD, DMC, CM), Clinical Neuroimaging Laboratory, National Centre for Biomedical Engineering (NCBES) Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, School of Psychology (DWM, GD), and Department of Biochemistry (DWM, GD), National University of Ireland Galway, Galway; Neuropsychiatric Genetics Research Group (DWM, AC, GD), Department of Psychiatry and Trinity College Institute of Neuroscience, Trinity College, Dublin, Ireland; Psychiatry Research Center (FY, YT, STan, ZW, FF, JC), Beijing Huilongguan Hospital, Beijing; Chongqing Three Gorges Central Hospital (HX, STang), Chongqing; Zhumadian Psychiatry Hospital (HG, PW), Henan Province, Zhumadian; Luoyang Fifth People's Hospital (DW), Henan Province, Luoyang, China; Laboratory of Neuropsychiatry (FA, NB, PdR, MI, FP, GS), Department of Clinical and Behavioral Neurology, IRCCS Santa Lucia Foundation; Centro Fermi (FA, FP), Museo Storico della Fisica e Centro Studi e Ricerche "Enrico Fermi"; Dipartimento di Neuroscienze, Salute Mentale e Organi di Senso (NEMOS) (PdR), Faculty of Medicine and Psychology, and Department of Neurology and Psychiatry (PdR), Sapienza University of Rome, Rome; Department of Basic Medical Science, Neuroscience and Sense Organs (ABer), University of Bari "Aldo Moro," Bari; Istituto Di Ricovero e Cura a Carattere Scientifico Casa Sollievo della Sofferenza (ABo, ADG), San Giovanni Rotondo, Italy; Centre

for Addiction and Mental Health (EWD, DR, ANV), Toronto, Canada; Departments of Psychosis Studies (SCi, JR, PD, RM, TRM, ASi) and Neuroimaging (DD), Institute of Psychiatry, Psychology and Neuroscience, King's College London; National Institute for Health Research Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust (PD), London; Department of Psychology (DD), City, University of London, London; Division of Psychiatry (EN, AMM, HCW, SML), Centre for Cognitive Ageing and Cognitive Epidemiology (SPH, AMM), and Department of Psychology (SPH), University of Edinburgh, Edinburgh, United Kingdom; University of Basel Psychiatric Hospital (SB, LE, FHa, AR-R, RSm), Basel, Switzerland; Department of Psychiatry (JSK) and Yeongseon Student Support Center (J-YY), Seoul National University College of Medicine; Department of Brain & Cognitive Sciences (JSK), College of Natural Sciences, Seoul National University; Seoul National University Hospital (J-YY), Seoul, Republic of Korea; Mental Health Research Center (IL, AST, VK); Children's Clinical and Research Institute of Emergency Surgery and Trauma (TA), Moscow, Russia; Laboratory of Psychiatric Neuroimaging, Laboratórios de Investigação Médica 21 (GFB, PGPR, MHS, MVZ), Department of Psychiatry, Faculty of Medicine, and Center for Interdisciplinary Research on Applied Neurosciences (GFB, PGPR, MHS, MVZ), University of São Paulo, São Paulo, Brazil; National Institute of Mental Health (CH, ASK, FS, DT), Klecany; MR Unit (ASK), Department of Diagnostic and Interventional Radiology, Institute for Clinical and Experimental Medicine, Prague; and Institute of Computer Science (DT), Czech Academy of Sciences, and Faculty of Electrical Engineering (DT), Czech Technical University in Prague, Prague, Czech Republic; Department of Psychiatry (FMH, DJS, HST, AU), Groote Schuur Hospital, University of Cape Town; Medical Research Council Unit on Risk & Resilience in Mental Disorders (DJS), Department of Psychiatry, University of Cape Town; Medical Research Council Unit on Risk & Resilience in Mental Disorders (AU), Department of Psychiatry, Stellenbosch University, Cape Town, South Africa; and Research Group in Psychiatry (CL-J), Department of Psychiatry, Faculty of Medicine, Universidad de Antioquia, Medellín, Colombia.

Members of the Karolinska Schizophrenia Project: Lars Farde (Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, and Stockholm County Council, Stockholm, Sweden), Lena Flyckt (Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, and Stockholm County Council, Stockholm, Sweden), Göran Engberg (Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden), Sophie Erhardt (Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden), Helena Fatouros-Bergman (Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, and Stockholm County Council, Stockholm, Sweden), Simon Cervenka (Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, and Stockholm County Council, Stockholm, Sweden), Lilly Schwieler (Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden), Fredrik Piehl (Neuroimmunology Unit, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden), Ingrid Agartz (Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, and Stockholm County Council, Stockholm, Sweden), K.G. Jepsen Centre for Psychosis Research, Division of Mental Health and Addiction, University of Oslo; Department of Psychiatry Research, Diakonhjemmet Hospital, Oslo, Norway; Karin Collste (Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, and Stockholm County Council, Stockholm, Sweden), Paulina Victorsson (Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, and Stockholm County Council, Stockholm, Sweden), Anna Malmqvist (Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden), Mikael Hedberg (Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden), and Funda Orhan (Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden).

Address correspondence to Theo G.M. van Erp, Ph.D., Department of Psychiatry and Human Behavior, University of California, Irvine, School of Medicine, 5251 California Avenue, Suite 240, Irvine, CA 92617; E-mail: tvanerp@uci.edu.

Received Sep 27, 2017; revised Apr 19, 2018; accepted Apr 20, 2018.

Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.biopsych.2018.04.023>.

REFERENCES

- Goghari VM, Truong W, Spilka MJ (2015): A magnetic resonance imaging family study of cortical thickness in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 168:660–668.
- Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, *et al.* (2003): Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry* 60:878–888.
- Thompson PM, Schwartz C, Toga AW (1996): High-resolution random mesh algorithms for creating a probabilistic 3D surface atlas of the human brain. *Neuroimage* 3:19–34.
- Miller MI, Massie AB, Ratnanather JT, Botteron KN, Csemansky JG (2000): Bayesian construction of geometrically based cortical thickness metrics. *Neuroimage* 12:676–687.
- Kabani N, Le Goualher G, MacDonald D, Evans AC (2001): Measurement of cortical thickness using an automated 3-D algorithm: A validation study. *Neuroimage* 13:375–380.
- Zijdenbos AP, Forghani R, Evans AC (2002): Automatic “pipeline” analysis of 3-D MRI data for clinical trials: Application to multiple sclerosis. *IEEE Trans Med Imaging* 21:1280–1291.
- Lerch JP, Evans AC (2005): Cortical thickness analysis examined through power analysis and a population simulation. *Neuroimage* 24:163–173.
- Ad-Dab'bagh Y, Einarson D, Lyttelton O, Muehlboeck J-S, Mok K, Ivanov O, *et al.* (2006): The CIVET image-processing environment: A fully automated comprehensive pipeline for anatomical neuroimaging research. In: Corbetta M, editor. *Proceedings of the 12th Annual Meeting of the Organization for Human Brain Mapping*. Florence, Italy: NeuroImage.
- Fischl B (2012): FreeSurfer. *Neuroimage* 62:774–781.
- Stein JL, Medland SE, Vasquez AA, Hibar DP, Senstad RE, Winkler AM, *et al.* (2012): Identification of common variants associated with human hippocampal and intracranial volumes. *Nat Genet* 44:552–561.
- Thompson PM, Stein JL, Medland SE, Hibar DP, Vasquez AA, Renteria ME, *et al.* (2014): The ENIGMA Consortium: Large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging Behav* 8:153–182.
- Thompson PM, Andreassen OA, Arias-Vasquez A, Bearden CE, Boedhoe PS, Brouwer RM, *et al.* (2017): ENIGMA and the individual: Predicting factors that affect the brain in 35 countries worldwide. *Neuroimage* 145:389–408.
- Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, *et al.* (2009): Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex* 19:2728–2735.
- Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, *et al.* (2010): Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage* 53:1135–1146.
- Rimol LM, Hartberg CB, Nesvåg R, Fennema-Notestine C, Hagler DJ Jr, Pung CJ, *et al.* (2010): Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. *Biol Psychiatry* 68:41–50.
- van Haren NEM, Schnack HG, Cahn W, van den Heuvel MP, Lepage C, Collins L, *et al.* (2011): Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry* 68:871–880.
- Sugihara G, Oishi N, Son S, Kubota M, Takahashi H, Murai T (2017): Distinct patterns of cerebral cortical thinning in schizophrenia: A neuroimaging data-driven approach. *Schizophr Bull* 43:900–906.
- Schultz CC, Koch K, Wagner G, Roebel M, Nenadic I, Schachtzabel C, *et al.* (2010): Complex pattern of cortical thinning in schizophrenia: Results from an automated surface based analysis of cortical thickness. *Psychiatry Res* 182:134–140.
- Narr KL, Toga AW, Szeszko P, Thompson PM, Woods RP, Robinson D, *et al.* (2005): Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. *Biol Psychiatry* 58:32–40.
- Narr KL, Bilder RM, Toga AW, Woods RP, Rex DE, Szeszko PR, *et al.* (2005): Mapping cortical thickness and gray matter concentration in first episode schizophrenia. *Cereb Cortex* 15:708–719.

21. Fornito A, Yücel M, Wood SJ, Adamson C, Velakoulis D, Saling MM, *et al.* (2008): Surface-based morphometry of the anterior cingulate cortex in first episode schizophrenia. *Hum Brain Mapp* 29:478–489.
22. Sun D, Stuart GW, Jenkinson M, Wood SJ, McGorry PD, Velakoulis D, *et al.* (2009): Brain surface contraction mapped in first-episode schizophrenia: A longitudinal magnetic resonance imaging study. *Mol Psychiatry* 14:976–986.
23. Crespo-Facorro B, Roiz-Santiañez R, Pérez-Iglesias R, Rodríguez-Sánchez JM, Mata I, Tordesillas-Gutiérrez D, *et al.* (2011): Global and regional cortical thinning in first-episode psychosis patients: Relationships with clinical and cognitive features. *Psychol Med* 41:1449–1460.
24. Lesh TA, Tanase C, Geib BR, Niendam TA, Yoon JH, Minzenberg MJ, *et al.* (2015): A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. *JAMA Psychiatry* 72:226–234.
25. Baribeau DA, Anagnostou E (2013): A comparison of neuroimaging findings in childhood onset schizophrenia and autism spectrum disorder: A review of the literature. *Front Psychiatry* 4:175.
26. Ordóñez AE, Lüscher ZI, Gogtay N (2016): Neuroimaging findings from childhood onset schizophrenia patients and their non-psychotic siblings. *Schizophr Res* 173:124–131.
27. Voets NL, Hough MG, Douaud G, Matthews PM, James A, Winmill L, *et al.* (2008): Evidence for abnormalities of cortical development in adolescent-onset schizophrenia. *Neuroimage* 43:665–675.
28. Venkatasubramanian G, Jayakumar PN, Gangadhar BN, Keshavan MS (2008): Automated MRI parcellation study of regional volume and thickness of prefrontal cortex (PFC) in antipsychotic-naïve schizophrenia. *Acta Psychiatr Scand* 117:420–431.
29. Rais M, Cahn W, Schnack HG, Hulshoff Pol HE, Kahn RS, van Haren NEM (2012): Brain volume reductions in medication-naïve patients with schizophrenia in relation to intelligence quotient. *Psychol Med* 42:1847–1856.
30. Liu X, Lai Y, Wang X, Hao C, Chen L, Zhou Z, *et al.* (2014): A combined DTI and structural MRI study in medicated-naïve chronic schizophrenia. *Magn Reson Imaging* 32:1–8.
31. van Lutterveld R, van den Heuvel MP, Diederens KJM, de Weijer AD, Begemann MJH, Brouwer RM, *et al.* (2014): Cortical thickness in individuals with non-clinical and clinical psychotic symptoms. *Brain* 137:2664–2669.
32. Haller S, Borgwardt SJ, Schindler C, Aston J, Radue EW, Riecher-Rössler A (2009): Can cortical thickness asymmetry analysis contribute to detection of at-risk mental state and first-episode psychosis? A pilot study. *Radiology* 250:212–221.
33. Sun D, Phillips L, Velakoulis D, Yung A, McGorry PD, Wood SJ, *et al.* (2009): Progressive brain structural changes mapped as psychosis develops in “at risk” individuals. *Schizophr Res* 108:85–92.
34. Jung WH, Kim JS, Jang JH, Choi J-S, Jung MH, Park J-Y, *et al.* (2011): Cortical thickness reduction in individuals at ultra-high-risk for psychosis. *Schizophr Bull* 37:839–849.
35. Shin KS, Jung WH, Kim JS, Jang JH, Hwang JY, Chung CK, Kwon JS (2012): Neuromagnetic auditory response and its relation to cortical thickness in ultra-high-risk for psychosis. *Schizophr Res* 140:93–98.
36. Tognin S, Pettersson-Yeo W, Valli I, Hutton C, Woolley J, Allen P, *et al.* (2013): Using structural neuroimaging to make quantitative predictions of symptom progression in individuals at ultra-high risk for psychosis. *Front Psychiatry* 4:187.
37. Tognin S, Riecher-Rössler A, Meisenzahl EM, Wood SJ, Hutton C, Borgwardt SJ, *et al.* (2014): Reduced parahippocampal cortical thickness in subjects at ultra-high risk for psychosis. *Psychol Med* 44:489–498.
38. Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TGM, *et al.* (2015): Progressive reduction in cortical thickness as psychosis develops: A multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biol Psychiatry* 77:147–157.
39. Buchy L, Barbato M, Makowski C, Bray S, MacMaster FP, Deighton S, Addington J (2017): Mapping structural covariance networks of facial emotion recognition in early psychosis: A pilot study. *Schizophr Res* 189:146–152.
40. van Erp TGM, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, *et al.* (2016): Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Mol Psychiatry* 21:547–553.
41. Okada N, Fukunaga M, Yamashita F, Koshiyama D, Yamamori H, Ohi K, *et al.* (2016): Abnormal asymmetries in subcortical brain volume in schizophrenia. *Mol Psychiatry* 21:1460–1466.
42. Cahn W, Rais M, Stigter FP, van Haren NEM, Caspers E, Hulshoff Pol HE, *et al.* (2009): Psychosis and brain volume changes during the first five years of schizophrenia. *Eur Neuropsychopharmacol* 19: 147–151.
43. Gogtay N, Weisinger B, Bakalar JL, Stidd R, Fernandez de la Vega O, Miller R, *et al.* (2012): Psychotic symptoms and gray matter deficits in clinical pediatric populations. *Schizophr Res* 140:149–154.
44. Oertel-Knöchel V, Knöchel C, Rotarska-Jagiela A, Reinke B, Prvulovic D, Haenschel C, *et al.* (2013): Association between psychotic symptoms and cortical thickness reduction across the schizophrenia spectrum. *Cereb Cortex* 23:61–70.
45. Padmanabhan JL, Tandon N, Haller CS, Mathew IT, Eack SM, Clementz BA, *et al.* (2015): Correlations between brain structure and symptom dimensions of psychosis in schizophrenia, schizoaffective, and psychotic bipolar I disorders. *Schizophr Bull* 41:154–162.
46. Xiao Y, Lui S, Deng W, Yao L, Zhang W, Li S, *et al.* (2013): Altered cortical thickness related to clinical severity but not the untreated disease duration in schizophrenia. *Schizophr Bull* 41:201–210.
47. Walton E, Hibar DP, van Erp TGM, Potkin SG, Roiz-Santiañez R, Crespo-Facorro B, *et al.* (2017): Positive symptoms associate with cortical thinning in the superior temporal gyrus via the ENIGMA Schizophrenia consortium. *Acta Psychiatr Scand* 135:439–447.
48. Walton E, Hibar DP, van Erp TGM, Potkin SG, Roiz-Santiañez R, Crespo-Facorro B, *et al.* (2018): Prefrontal cortical thinning links to negative symptoms in schizophrenia via the ENIGMA consortium. *Psychol Med* 48:82–94.
49. Navari S, Dazzan P (2009): Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychol Med* 39:1763–1777.
50. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreassen NC, Borgwardt S (2013): Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev* 37:1680–1691.
51. Vita A, De Peri L, Deste G, Barlati S, Sacchetti E (2015): The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: Does the class matter? A meta-analysis and meta-regression of longitudinal magnetic resonance imaging studies. *Biol Psychiatry* 78:403–412.
52. Kay SR, Fiszbein A, Opler LA (1987): The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 13:261–276.
53. Andreasen NC (1984): Scale for the Assessment of Negative Symptoms: SANS. Iowa City: University of Iowa.
54. Andreasen N (1984): The Scale for the Assessment of Positive Symptoms (SAPS). Iowa City: University of Iowa.
55. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, *et al.* (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 31:968–980.
56. Viechtbauer W (2010): Conducting meta-analyses in R with the metafor Package. *J Stat Softw* 36:1–48.
57. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol* 57:289–300.
58. Thompson PM, Bartzokis G, Hayashi KM, Klunder AD, Lu PH, Edwards N, *et al.* (2009): Time-lapse mapping of cortical changes in schizophrenia with different treatments. *Cereb Cortex* 19: 1107–1123.
59. Ho B-C, Andreasen NC, Ziebell S, Pierson R, Magnotta V (2011): Long-term antipsychotic treatment and brain volumes: A longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry* 68:128–137.
60. Ansell BR, Dwyer DB, Wood SJ, Bora E, Brewer WJ, Proffitt TM, *et al.* (2015): Divergent effects of first-generation and second-generation

- antipsychotics on cortical thickness in first-episode psychosis. *Psychol Med* 45:515–527.
61. Hedman AM, van Haren NEM, van Baal GCM, Brouwer RM, Brans RGH, Schnack HG, *et al.* (2016): Heritability of cortical thickness changes over time in twin pairs discordant for schizophrenia. *Schizophr Res* 173:192–199.
 62. Lieberman JA (2005): Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry* 62:361.
 63. Vernon AC, Crum WR, Lerch JP, Chege W, Natesan S, Modo M, *et al.* (2014): Reduced cortical volume and elevated astrocyte density in rats chronically treated with antipsychotic drugs—linking magnetic resonance imaging findings to cellular pathology. *Biol Psychiatry* 75:982–990.
 64. Takahashi T, Wood SJ, Soulsby B, McGorry PD, Tanino R, Suzuki M, *et al.* (2009): Follow-up MRI study of the insular cortex in first-episode psychosis and chronic schizophrenia. *Schizophr Res* 108:49–56.
 65. Lee S-H, Niznikiewicz M, Asami T, Otsuka T, Salisbury DF, Shenton ME, McCarley RW (2016): Initial and progressive gray matter abnormalities in insular gyrus and temporal pole in first-episode schizophrenia contrasted with first-episode affective psychosis. *Schizophr Bull* 42:790–801.
 66. Takahashi T, Wood SJ, Yung AR, Phillips LJ, Soulsby B, McGorry PD, *et al.* (2009): Insular cortex gray matter changes in individuals at ultra-high-risk of developing psychosis. *Schizophr Res* 111:94–102.
 67. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW (2003): Mapping cortical change across the human life span. *Nat Neurosci* 6:309–315.
 68. Birnbaum R, Weinberger DR (2017): Genetic insights into the neurodevelopmental origins of schizophrenia. *Nat Rev Neurosci* 18:727–740.
 69. Chen EY, Hui CL, Lam MM, Chiu CP, Law CW, Chung DW, *et al.* (2010): Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: Randomised controlled trial. *BMJ* 341:c4024.
 70. Tiihonen J, Wahlbeck K, Lönnqvist J, Klaukka T, Ioannidis JPA, Volavka J, Haukka J (2006): Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: Observational follow-up study. *BMJ* 333:224.
 71. Hibar DP, Westlye LT, Doan NT, Jahanshad N, Cheung JW, Ching CRK, *et al.* (2018): Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. *Mol Psychiatry* 23:932–942.
 72. Schmaal L, Hibar DP, Sämann PG, Hall GB, Baune BT, Jahanshad N, *et al.* (2017): Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. *Mol Psychiatry* 22:900–909.